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PROBLEM OF CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

Rheumatoid arthritis is characterized by a high frequency of adverse cardiovascular events that cannot be explained only by the presence of classical risk factors.

The aim of the study – assessment of cardiovascular risk and fatal cardiovascular events according to the classical cardiovascular risk factors, as well as analysis of additional cardiovascular risk factors in patients with RA.

Materials and methods. We examined 56 patients with RA (38 women and 18 men) aged 28–65 years (mean age was (48,7±9,52) years). The average duration of disease was (9,8±2,7) years). 10-year coronary risk was evaluated by Framingham scale and the 10-year risk of fatal cardiovascular events – by SCORE scale. As additional risk factors, levels of C-reactive protein, tumor necrosis factor alpha, fibrinogen, platelet counts in peripheral blood, the activity of antithrombin III, activated partial thromboplastin time, the level of circulating endothelial cells and endothelial function (with Doppler examination of the brachial artery in the samples with reactive hyperemia and nitroglycerin) were investigated. The control group included 30 healthy people matched for age and sex with the main group.

Results. CHD risk and fatal cardiovascular events in RA patients, calculated taking into account only the classic risk factors, are close to their general population rate, which is contrary to clinical studies. Analysis of additional risk factors allowed to reveal in patients with RA the presence of signs of endothelium damage and dysfunction and increased prothrombogenic potential, which were directly related to the activity of systemic inflammation.

Conclusion. Presence of chronic systemic inflammation, endothelial dysfunction and changes in the haemostatic system affects the development of high cardiovascular risk in RA, and hence, they must be taken into account when evaluating cardiovascular risk.

Keywords: rheumatoid arthritis, cardiovascular risk, hemostasis system, systemic inflammation, endothelial dysfunction.

According to the recent scientific data, the importance of cardiovascular disease as the main cause of death in patients with rheumatoid arthritis (RA) [4] is determined by its ability to accelerate the development of atherosclerosis and give the essential features of its pathogenesis [2, 10]. This is manifested by asymptomatic, in a majority number of cases, nature of the clinical course, severe instability of atheromatous plaques, as well as the acute onset of clinical manifestations. A distinctive feature of cardiovascular disease in RA is a high risk of its development in young people and women, as well as increased mortality rate among subjects with low body mass index (less than 20 kg/m2) [3].

Reasons for the development and accelerated progression of atherosclerosis in patients with RA has not been fully clarified. It is shown that the pathogenesis of these processes in RA patients is determined not only by the traditional risk factors (dyslipidemia, diabetes mellitus (DM), arterial hypertension (AH), increased body mass index (BMI), reduced physical activity [1, 16]), but by the presence of specific factors, first of all - chronic systemic inflammation of high gradation [2]. Several studies proved that systemic inflammation and impaired function of the immune system are among the leading risk factors of cardiovascular disease in RA, and the endothelium is the primary target of the inflammatory mediators action [8, 10].

Endothelial damage in patients with RA is mainly due to the direct action of inflammatory mediators; as a result of this there are many mature cast-off endotheliocites in peripheral blood appears. Unlike traditional course of atherosclerosis with a primary lesion of the aorta and major arteries in RA noted diffuse damage of the arterial system with distinct functional attributes of arteriosclerosis and microvasculature involvement [6]. Results of a few coronary arteries direct studies in patients with RA suggests that the traditional atherosclerosis pathogenic factors of coronary artery damage in patients with RA cause it's development in less than 50%; at the same time, dominates direct proatherogenic actions of inflammatory mediators [13]. Pro-inflammatory cytokines plays the key role in the relationship between systemic inflammation and the development of cardiovascular events. Presence of systemic inflammation in patients with RA and increased levels of proinflammatory cytokines in synovial fluid and in the blood

facilitates vascular wall infiltration by monocytes and atherogenic factors activation [10].

Thus, there is reason to believe that the only classical risk factors evaluation is insufficient to determine cardiovascular risk (CVR) in patients with RA. However, to date there are practically no data on a integrated assessment of classical and other cardiovascular risk factors in RA, which makes interpretation of the results uncertain stratification CVR using conventional techniques in these patients.

The aim of the study – assessment of cardiovascular risk and fatal cardiovascular events according to the classical cardiovascular risk factors, as well as analysis of additional cardiovascular risk factors in patients with RA.

Materials and methods

We examined 56 patients with RA (38 women and 18 men) aged 28–65 years (mean age – (48,7±9,52) years). The average duration of the disease was (9,8±2,7) years). The diagnosis of RA was set according to the classification criteria of the American College of Rheumatology and the order of MH of Ukraine № 676 of 12.10.2006. Most of the patients were seropositive for rheumatoid factor – 83,44%. The proportion of patients with seronegative variant in the structure of the analyzed patients was – 16,56%. In all patients, along with performing standard clinical and laboratory diagnostics, we conducted clinical assessment of joints damage, an overall assessment of disease activity and functional abilities of the patient, followed by a quantitative assessment of RA activity using composite index DAS 28. As basic therapy Methotrexate at a dose of (12,5±2,5) mg/week in combination with folic acid was administered. The study excluded patients who had previously biologically active drugs intake.

All patients were screened with arterial hypertension (AH) and the classic risk factors for cardiovascular disease: smoking, hyper-and dyslipidemia (levels of total cholesterol (TC), high density lipoprotein (HDL), triglycerides (TG) with the calculation of level of low-density lipoprotein (LDL) by W.T. Friedewald et al (1972) and atherogenic coefficient (AC), overweight (defined at a value of body mass index ≥25 kg/m2), heredity, diabetes. Diagnosis of arterial hypertension was set on the ground of elevated levels of blood pressure (BP)>140 and 90 mm Hg, obtained three times (during hospitalization or according to medical records).

Using Framingham scale (developed on the basis of population-based The Framingham Heart Study (Wilson PW et al., 1998) for all patients we calculated 10-year coronary risk (the risk of coronary heart disease (CHD). This scale takes into account age, gender, total cholesterol and HDL cholesterol, blood pressure, presence of diabetes, and smoking status. In addition, we calculated 10-year fatal risk (the risk of death from coronary heart disease, atherosclerosis, cerebral and peripheral arteries) using SCORE table (Systemic Coronary Risk Evaluation) (Conroy RM et al., 2003). This scale takes into account age, gender, total cholesterol, systolic blood pressure and smoking status. The risk of fatal complications according to the SCORE Scale is considered low, if it is <5%, with a high value in the range of from 5 to 10%, and very high if it exceeds 10%. Markers of systemic inflammation, haemostatic parameters, markers of endothelial damage and dysfunction were determined as additional cardiovascular risk factors.

The concentration of C-reactive protein (CRP) was determined by using immunoturbometrik diagnostic kit «BioSystems» and multifunction biochemical analyzer «Cobas Fara»; fibrinogen, platelets in the peripheral blood, the activity of antithrombin III, the activated partial thromboplastin time (APTT) were determined using standard methods. Serum cytokine levels were determined by enzyme-linked immunosorbent assay (ELISA) using a commercial test kits and reagents "Cytokine" (St. Petersburg). Determining of the circulating endothelial cells (CEC) levels in peripheral blood (marker of endothelial damage) was performed by the method of J. Hladovec (1978). Endothelium functional state was assessed using ultrasonic methods for determining of the endothelium dependent vasodilatation (EDVD) of the brachial artery (BA) with mechanical stimulation of blood flow and nitroglycerin (according to the Guidelines for the ultra-sound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery (2002).

The obtained data were processed by means of «Microsoft Excel XP» and Statistika 6.0 («StatSoft», USA) programs. To describe the normal distribution of the data sample we used the average value of the characteristic (M) and standard error (m), the confidence factor (p). Difference of the results considered as a significant at p-level <0,05. Relationship between parameters was assessed by means of Spearman rank correlation method.

Results and discussion

Arterial hypertension was determined in 45% of patients; in all cases increased blood pressure does not exceed the second degree. 38,4% of patients received adequate antihypertensive therapy. According to the literature data, for persons with RA characteristic is the high prevalence of hypertension. It was shown that at approximately 56% of individuals with RA without evidence of cardiovascular disease systolic blood pressure exceeds 140 mmHg. In the study involving 400 patients with RA, the presence of arterial hypertension was found in 70,5% of patients. In patients with RA arterial hypertension

was characterized by high resistance to therapy, and of 60,6% of patients who were on antihypertensive therapy, optimal control of blood pressure (BP) was achieved in only 22% [12].

Obtained screening results of the classic cardiovascular risk factors are represented in Table 1.

Analysis of lipid disorders showed high frequency of detection of reduced levels of HDL cholesterol (61%), at a relatively low (13%) detection rate of hypercholesterolemia. Lipid profile of examined patients and subjects of control group represented in Table 2.

In patients with RA total cholesterol level was significantly lower than those one at the persons of control group and the levels of LDL cholesterol and TG were comparable with those of the healthy individuals. At the same time, in RA patients we determined significant decrease of anti-atherogenic HDL cholesterol that appear is the cause of significantly greater atherogenic coefficient value compared to the same index in the control group.

According to the results of most studies, traditional parameters of lipid profile in patients with CAD, naturally did not differ in the presence of concomitant RA. In this case the data are not always consistent with the current knowledge of the pathogenesis of atherosclerosis, and sometimes contradict them. Thus, in most studies there was no significant disorder of lipid profile (total cholesterol content, TG, LDL and HDL) in patients with RA even on the basis of pronounced atherosclerosis, with increased concentration of small LDL particles and reduced concentration of small HDL particles, which were in direct correlation with the severity of the disease, inflammation activity and blood levels of CRP [4]. Such a pro-atherogenic lipoprotein phenotype characterized by systemic inflammation and is a natural component of the acute phase response, which significantly increases cardiovascular risk regardless of the level of total cholesterol and LDL-C [11].

Mean BMI was (23,4±4,6) kg/m2: a majority (54%) of patients had normal weight (BMI (18,5–24,9) kg/m2), 21% of patients - deficit (BMI< 18,5 kg/m2), 25% of patients – the excess weight (BMI>25 kg/m2), including 5% – obesity (BMI>30 kg/m2). 10-year coronary risk by Framingham scale in patients with RA was 4,0% (from 3,0 to 7,5), which was significantly lower than the risk for the population of comparable age and sex without RA, calculated on the basis of data of The Framingham Heart Study – 5,0 (3,0 to 11,0)%, p<0,05. 10-year risk of fatal cardiovascular events by SCORE scale in studied patients was 1,0 (1,0 to 2,0)%, which can be considered as low-risk. However, 10-year fatal risk ≥5% (5 to 7%) was reported only in 5 patients [1].

In this connection, only classical risk factors assessing leads to the conclusion that in patients with RA risk of CHD, as well as the risk of fatal cardiovascular events is low, and at least comparable with population one. This is clearly contrary to the above

Table 1

The frequency of classical cardiovascular risk factors revealing in examined patients (%)

Risk factor	Frequency, %
Smoking	11
Hypercholesterolemia (TC ≥5,0 mmol/l)	13
Low level of HDL cholesterol (<1 mmol/l for men and <1,2 mmol/l for women)	61
High level of LDL cholesterol (≥3,0 mmol/l)	22
Hypertriglyceridemia (triglycerides level ≥1,7 mmol/l)	13
Overweight (BMI ≥25kg/m2)	23
Family history of early cardio-vascular disease development	24
Diabetes mellitus	1

Table 2

Lipid profile in patients with RA and in the control group

Parameter	RA	Control
TC, mmol/l	4,03±0,45*	4,87±0,92
LDL cholesterol, mmol/l	2,47±0,83	2,71±0,89
HDL cholesterol, mmol/l	0,99±0,29*	1,22±0,36
TG, mmol/l	1,19±0,40	1,18±0,84
Atherogenic coefficient	3,27±1,21*	2,77±0,98

Note: * – *significance of parameters differences comparing with control at p<0,05–0,001*

Table 3

Additional cardiovascular risk factors in a group of patients with RA

Parameter	Control	RA
CRP, mg/l	4,2±0,27	11,67±1,52*
TNF-α, pg/ml	22,4±3,18	35,7±2,67*
Fibrinogen, gr/l	3,27±1,8	7,2±2,4*
Platelets, 109/l	245,8±37,2	351,2±26,4
Activity of antithrombin III, %	87,8±8,4	90,6±13,3
Activated partial thromboplastin time, sec	35,1±1,7	27,1±1,5*
BA EDVD, %	14,72±0,78	12,26±0,56
BA ENDVD, %	20,21±2,34	25,86±0,92*
CEC, 104/L	4,0 [3,5; 7,5]	5,0 [3,0; 8,0]*

Note: * – – *significance of parameters differences comparing with control at p<0,05–0,001*

data concerning the increased incidence of adverse cardiovascular events in patients with RA. In this connection analysis of additional cardiovascular risk factors isparticularly important (Table 3).

CRP level >10 mg/l, which is considered in recent years as one of the major cardiovascular risk factor, was revealed in 64% of patients; such fact is quite natural in view of the inflammatory nature of RA. In patients with rheumatoid arthritis TNF-α levels were significantly greater (p<0,001) in comparison with the control. Self importance of inflammation as an independent mechanism of atherogenesis is shown in a study in which a CRP level of less than 1, 1 to 3 and more than 3 mg/l was an indicator of low, moderate and high cardiovascular risk. Analysis of frequency of myocardial infarction, stroke, coronary vascularization or cardiac death in 27939 healthy women found that the value of CRP increases linearly in the range from 1,0 to 7,6, starting from the lowest levels of CRP content of 0,5 mg/l to 20 mg/l and above [14]. And the presence of high gradation chronic systemic inflammation in patients with RA determines increased cardiovascular mortality, even after effective control of pro-atherogenic factors such as dyslipidemia, hypertension, smoking, diabetes [9].

Fibrinogen levels in patients with RA are also quite expectedly higher than in the control group (p<0,001). There was high and medium levels of platelets; thrombocytosis (platelet count of more than 320 · 109/l) was observed in 54% of patients. Antithrombin III activity in RA was comparable to the activity of this factor in the control group (p>0,05). Activated partial thromboplastin time, on the contrary, in subjects with RA was significantly lower (p<0,001). The presence of the relationship between activity of systemic inflammation and changes in the haemostatic system shows significant correlation between levels of CRP and TNF-α with fibrinogen level (r=0,49 and r=0,52 at p<0,001), platelet count (r=0,26 and r=0,36, p<0,05), activated partial thromboplastin time (r=0,35 and r=0,42, p<0,01), and the erythrocyte sedimentation rate with fibrinogen levels (r=0,594, p<0,001), and activated partial thromboplastin time (r=0,46, p<0,001).

Thus, in patients with RA, together with increased levels of acute-phase parameters reflecting the activity of systemic inflammation, there is an increasing of thrombogenic potential which is manifested with high levels of fibrinogen and platelets with simultaneous activated partial thromboplastin time decreasing. These changes may contribute to an increased risk of thrombosis and related adverse cardiovascular events.

There was no significant differences in EDVD level between studied groups, but the proportion of patients with reduced BA EDVD (<10%) was more greater in the group of RA than in the control group (47 and 18%, accordingly, p<0,01). Contrariwise, BA ENDVD was significantly greater in patients with RA. We suppose that the increased reactivity of the vascular wall in response to nitroglycerin in patients with RA may be the indirect evidence of deficiency of endogenous nitric oxide. Investigation of immune-inflammation activity influence on endothelial vasomotor function revealed a significant inverse correlation between BA ENDVD and TNF-α (r= −0,46, p<0,01) and CRP (r=−0,48, p<0,05).

In the group of patients with RA we revealed significantly greater level of CEC – endothelium damage marker. CEC level in RA patients significantly correlated with erythrocyte sedimentation rate (r=0,32, p<0,05).

So, in patients with RA signs of endothelial damage (CEC) and its dysfunction were determined (reduced BA EDVD was revealed in 47% of patients and BA ENDVD exceeds not only the BA EDVD, but the corresponding levels of BA EDVD in healthy individuals).

According to the literature data, arterial wall stiffness increasing is one of the independent factors of cardiovascular mortality, especially in

patients with RA [15]. These changes are associated with high activity of systemic inflammation: proinflammatory cytokines levels increasing in the blood [5]. The key role of inflammation in the pathogenesis of atherosclerosis and coronary heart disease in RA also confirmed by a significant reduction of cardiovascular and all-cause mortality rates in patients with severe RA treated with antibodies to TNF-α. Despite the fact that TNF-α blockers did not provide traditional atherogenesis factors influence (blood levels of total cholesterol and LDL), they have contributed to the normalization of endothelial function, to the impairment of vascular wall elasticity and insulin sensitivity; also they reduced the intima-media thickness of the carotid arteries [7].

Conclusions

1. CHD risk and fatal cardiovascular events in RA patients, calculated taking into account only the classic risk factors, are close to their general population rate, which is contrary to clinical studies.

2. Analysis of additional risk factors allowed to reveal in patients with RA the presence of signs of endothelium damage and dysfunction and increased prothrombogenic potential, which were directly related to the activity of systemic inflammation.

3. Presence of chronic systemic inflammation, endothelial dysfunction and changes in the haemostatic system affects the development of high cardiovascular risk in RA, and hence, they must be taken into account when evaluating cardiovascular risk.

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ПРОБЛЕМА ОЦІНКИ КАРДІОВАСКУЛЯРНОГО РИЗИКУ У ХВОРИХ РЕВМАТОЇДНИМ АРТРИТОМ

Системні запальні захворювання характеризуються високою частотою несприятливих серцево-судинних подій, що не може бути пояснено тільки наявністю класичних факторів ризику.

Мета дослідження – оцінка серцево-судинного ризику і фатальних серцево-судинних подій за класичними факторами ризику, а також аналіз додаткових факторів серцево-судинного ризику у пацієнтів з РА.

Матеріал і методи. Обстежено 56 пацієнтів з ревматоїдним артритом (38 жінки і 18 чоловіків) віком 28–65 років (середній вік - (48,7±9,52) року). Середня тривалість захворювання склала (9,8±2,7) року). Оцінювали 10-річний коронарний ризик за Фрамінгемською шкалою і 10-річний ризик фатальних серцево-судинних подій за шкалою SCORE. З додаткових факторів ризику досліджували рівень С-реактвного протеїну, фактор некрозу пухлин альфа, фібриногену, тромбоцитів у периферичній крові, активність антитромбіну III, активований частковий тромбопластиновий час, рівень циркулюючих ендотеліальних клітин і функціональний стан ендотелію (при допплерографічному дослідженні плечової артерії у пробах з реактивною гіперемією і нітрогліцерином). Групу контролю склали 30 практично здорових осіб, порівнянних за віком і статтю з основною групою.

Результати. Кардіоваскулярний ризик у пацієнтів з ревматоїдним артритом, оцінюваний за класичними чинниками ризику, не перевищував середньопопуляційний рівень. Результати аналізу додаткових факторів ризику вказують на наявність у пацієнтів з ревматоїдним артритом ознак ушкодження, дисфункції ендотелію та підвищеного протромбогенного потенціалу, безпосередньо пов'язаних з активністю системного запалення.

Висновки. Наявність хронічного системного запалення, дисфункція ендотелію та зміни у системі гемостазу впливають на розвиток високого кардіоваскулярного ризику при ревматоїдному артриті і їх доцільно враховувати при його оцінці.

Ключові слова: ревматоїдний артрит, кардіоваскулярний ризик, система гемостазу, системне запалення, ендотеліальна дисфункція.

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ПРОБЛЕМА ОЦЕНКИ КАРДИОВАСКУЛЯРНОГО РИСКА У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

Ревматоидный артрит (РА) характеризуется высокой частотой неблагоприятных сердечно-сосудистых событий, что не может быть объяснено только наличием классических факторов риска.

Цель исследования – оценка сердечно-сосудистого риска и фатальных сердечно-сосудистых событий по классическим факторам риска, а также анализ дополнительных факторов сердечно-сосудистого риска у пациентов с РА.

Материал и методы. Обследовано 56 пациентов с РА (38 женщины и 18 мужчин) в возрасте 28–65 лет (средний возраст – (48,7±9,52) года). Средняя продолжительность заболевания составила (9,8±2,7) года). Оценивали 10-летний коронарный риск по Фрамингемской шкале и 10-летний риск фатальных сердечно-сосудистых событий по шкале SCORE. Из дополнительных факторов риска исследовали уровень С-реактвного протеина, фактор некроза опухолей альфа, фибриногена, тромбоцитов в периферической крови, активность антитромбина III, активированное частичное тромбопластиновое время, уровень циркулирующих эндотелиальных клеток и функциональное состояние эндотелия (при допплерографическом исследовании плечевой артерии в пробах с реактивной гиперемией и нитроглицерином). Группу контроля составили 30 практически здоровых лиц, сопоставимых по возрасту и полу с основной группой.

Результаты. Кардиоваскулярный риск у пациентов с ревматоидным артритом, оцениваемый по классическим факторам риска, не превышал среднепопуляционный уровень. Результаты анализа дополнительных факторов риска указывают на наличие у пациентов с ревматоидным артритом признаков повреждения, дисфункции эндотелия и повышенного протромбогенного потенциала, непосредственно связанных с активностью системного воспаления.

Выводы. Наличие хронического системного воспаления, дисфункция эндотелия и изменения в системе гемостаза влияют на развитие высокого кардиоваскулярного риска при ревматоидном артрите и их необходимо учитывать при его оценке.

Ключевые слова: ревматоидный артрит, кардиоваскулярный риск, система гемостаза, системное воспаление, эндотелиальная дисфункция